

Computational study of direct chemical phenol glycosylation mechanism

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Glycosylation is a chemical reaction between a carbohydrate and another molecule with any functional group which can act as a glycosyl acceptor forming *glycoconjugate* as a reaction product. Glycoconjugates are extremely important for different fields, including biochemistry, organic synthesis, pharmaceuticals, etc. [1]. This type of chemical species are extensively studied in terms of drug delivery and dietary supplements due to significant improve of solubility and bioavailability of different small biologically active molecules, such as flavonoids [2].

Nevertheless, classical organic synthesis of glycosylated flavonoids including flavonoid rutin contains multiple stages and is complicated by the necessity to protect flavonol molecules from oxidation in the liquid phase. Direct solid-state synthesis of glycosylated flavonol and its derivatives, if possible, may resolve this issue. Thus, the aim of this study is to evaluate the possible reaction path of flavonols with carbohydrates using a reaction between glucose and phenol as a simple model, calculate energy barriers and estimate stable products using modern DFT approach.

The present work provides a clear view of the reaction mechanism and particular path of phenol direct chemical glycosylation through the formation of glucose carbocation (C₁ carbocation with free *p*-orbital is attacked by phenyl -OH group), providing formation of C-O bond and H⁺ proton migration to the nearest functional group. All performed calculations prove the concept of possible direct glycosylation of flavonols in the solid state using mechanochemical synthesis, which coincides with our preliminary results on quercetin [3].

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